



(19)

Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 1 002 570 A1

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
24.05.2000 Bulletin 2000/21

(51) Int Cl.7: B01J 4/02, B01J 19/00,
B01L 3/02, B41J 2/23,
B41J 2/235, B41J 2/25,
B41J 2/265

(21) Application number: 98402906.6

(22) Date of filing: 20.11.1998

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE

- Dannoux, Thierry Luc Alain,
Corning Inc. Patent Dep
Corning, NY 14831 (US)

Designated Extension States:

AL LT LV MK RO SI

(71) Applicant: CORNING INCORPORATED
Corning, N.Y. 14831 (US)

(74) Representative: Marchant, James Ian
Elkington and Fife,
Prospect House,
8 Pembroke Road
Sevenoaks, Kent TN13 1XR (GB)

(72) Inventors:

- Root, David,
Corning Incorporated Patent Departm.
Corning, NY 14831 (US)

(54) Capillary transfer device for high density arrays

(57) A method and apparatus for printing high density biological or chemical arrays utilizes a plurality of rods (22) each housed within discrete a channel (12) of a multi-channelled form (50,61). The form (50,61) is shaped such that each channel (12) is capable of retaining liquid by capillary pressure force. The liquid is expelled from the channels (12) by extending the rods (22) beyond the output face of each channel (12). Each rod (22) retains a representative drop (40) of liquid from its respective channel (12) which is contacted to a substrate surface (36) causing transfer. Ideally, the rods (22) are all connected to a rear plate (76) thereby enabling simultaneous transfer of any number of liquid drops (40).

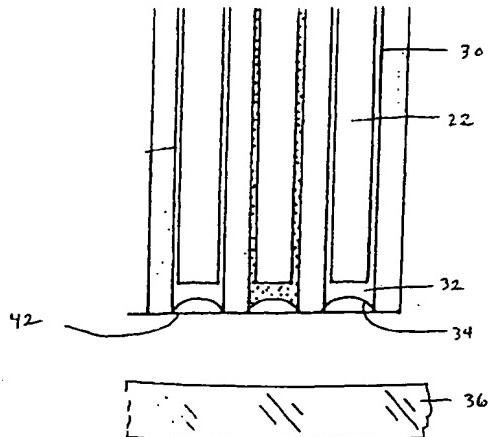


FIG. 3

BEST AVAILABLE COPY

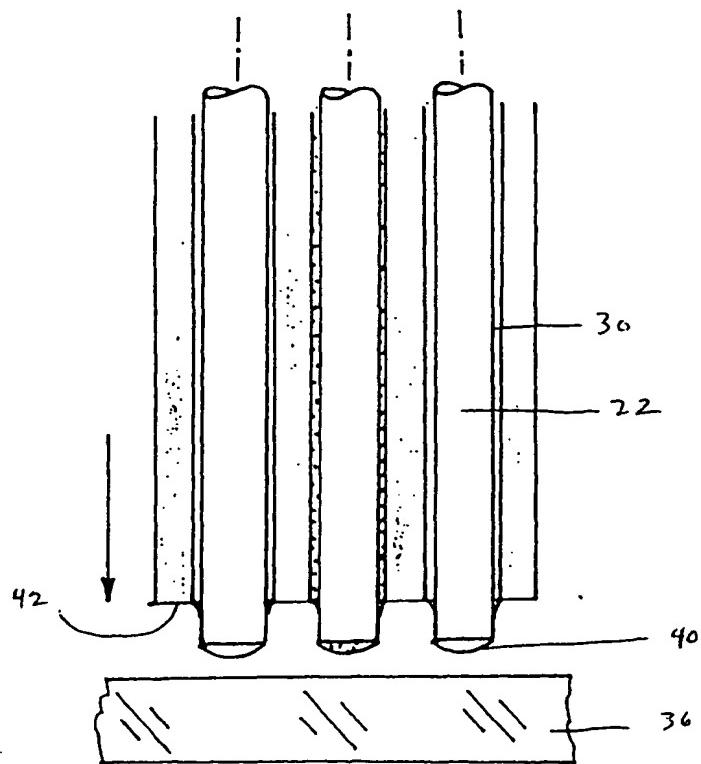


FIG. 4

Description**Field Of Invention**

[0001] The invention relates to a device and method for the printing of high density arrays for use in biological and chemical assays in the form of a device that can be used in sample transfer between a multi-channelled reservoir tool and a substrate.

Background of Invention

[0002] Hybridization is a hydrogen-bonding interaction between two nucleic acid strands that obey the Watson-Crick complementary rules. All other base pairs are mismatches that destabilize hybrids. Since a single mismatch decreases the melting temperature of a hybrid by up to 10° C, conditions can be found in which only perfect hybrids can survive. Hybridization comprises contacting the strands, one of which is usually immobilized on a solid support and the other usually bears a radioactive, chemiluminescent or fluorescent label, and then separating the resulting hybrids from the unreacted labeled strands by washing the support. Hybrids are recognized by detecting the label bound to the surface of the support.

[0003] Oligonucleotide hybridization is widely used to determine the presence in a nucleic acid of a sequence that is complimentary to the oligonucleotide probe. In many cases, this provides a simple, fast, and inexpensive alternative to conventional sequencing methods. Hybridization does not require nucleic acid cloning and purification, carrying out base-specific reactions, or tedious electrophoretic separations. Hybridization of oligonucleotide probes has been successfully used for various purposes, such as analysis of genetic polymorphisms, diagnosis of genetic diseases, cancer diagnostics, detection of viral and microbial pathogens, screening of clones, genome mapping and ordering of fragment libraries.

[0004] An oligonucleotide array is comprised of a number of individual oligonucleotide species tethered to the surface of a solid support in a regular pattern, each species in a different area, so that the location of each oligonucleotide is known. An array can contain a chosen collection of oligonucleotides, e.g., probes specific for all known clinically important pathogens or specific for all known clinically important pathogens or specific for all known sequence markers of genetic diseases. Such an array can satisfy the needs of a diagnostic laboratory. Alternatively, an array can contain all possible oligonucleotides of a given length n . Hybridization of a nucleic acid with such a comprehensive array results in a list of all its constituent n -mers, which can be used for unambiguous gene identification (e.g., in forensic studies), for determination of unknown gene variants and mutations (including the sequencing of related genomes once the sequence of one of them is known), for overlapping

clones, and for checking sequences determined by conventional methods. Finally, surveying the n -mers by hybridization to a comprehensive array can provide sufficient information to determine the sequence of a totally unknown nucleic acid.

[0005] Oligonucleotide arrays can be prepared by synthesizing all the oligonucleotides, in parallel, directly on the support, employing the methods of solid-phase chemical synthesis in combination with site-directing masks as described in US Pat. 5,510,270. Four masks with non-overlapping windows and four coupling reactions are required to increase the length of tethered oligonucleotides by one. In each subsequent round of synthesis, a different set of four masks is used, and this

[15] determines the unique sequence of the oligonucleotides synthesized in each particular area. Using an efficient photolithographic technique, miniature arrays containing as many as 10^5 individual oligonucleotides per cm^2 of area have been demonstrated.

[0006] Another technique for creating oligonucleotide arrays involves precise drop deposition using a piezoelectric pump as described in US Pat. 5,474,796. The piezoelectric pump delivers minute volumes of liquid to a substrate surface. The pump design is very similar to

[25] the pumps used in ink jet printing. This picopump is capable of delivering 50 micron diameter (65 picoliter) droplets at up to 3000 Hz and can accurately hit a 250 micron target. The pump unit is assembled with five nozzles array heads, one for each of the four nucleotides

[30] and a fifth for delivering activating agent for coupling. The pump unit remains stationary while droplets are fired downward at a moving array plate. When energized, a microdroplet is ejected from the pump and deposited on the array plate at a functionalized binding site. Different oligonucleotides are synthesized at each individual binding site based on the microdrop deposition sequence.

[0007] Another approach using arrays is the pin dipping method for parallel oligonucleotide synthesis. Geyseren, J. Org. Chem. 56, 6659 (1991). In this method, small amounts of solid support are fused to arrays of solenoid controlled polypropylene pins, which are sequentially dipped into trays of the appropriate reagents. The density of the arrays is limited by this process.

[0008] Further approaches to forming an array involve taking presynthesized oligonucleotide or cDNA sequences from separately prepared aqueous mixtures and transferring them to substrate either individually or in some small multiple. This may be accomplished for

[50] example by repeatedly contacting a substrate surface with typographic pins holding droplets, using ink jet printing mechanisms to lay down an array matrix, or by use of a pen plotter. These printing processes are limited by the time and expense required in transferring 10^3 or greater different sequence mixtures onto defined positions on a substrate.

[0009] Commonly assigned EPO application #####, incorporated herein by reference, discloses a capillary

reservoir device and method of printing an array of biomolecules. The tool is made up of a plurality of open ended channels collectively forming a matrix. The matrix has been redrawn and cut such that the pitch of the channels on the loading end is far larger than the pitch of the channels on the liquid delivery end. The upper portion of each channel serves as a reservoir, while the opposing end, which has been formed by the redrawing process, is diametrically sized such that liquid in the reservoir is retained by capillary pressure at the delivery end. Each channel is filled with a liquid solution preferably containing a different known biomolecule. The application discloses two methods of transferring drops of liquid from the channels of the liquid deposition tool to a substrate. In the first method, drops are forced directly out of the channels by some external force and contacted to the substrate directly. Unfortunately, this type of printing requires an environment of zero or negative capillary pressure. This may require the transfer to occur in an environmental immiscible liquid medium other than air.

[0010] The second method requires a typographic pin array in the form of a plate having a matrix of pins aligned such that each pin from the matrix fits into a corresponding channel from the output face of the reservoir device. The pin plate is contacted with the output face such that each pin enters each respective channel, contacts the liquid therein, and is removed. The pin tips each retain some volume of liquid from the channels by capillary force. The pin array is then contacted with a suitable substrate such that some volume of the liquid is transferred from the pins to the substrate. In order for the pin plate transfer method to work effectively, the pin plate must be constructed such that each pin exactly registers with a corresponding channel. If the array of channels making up the printing tool has been slightly deformed in any way during any of the steps of extrusion, sintering, or redrawing, the pin plate must be constructed to account for these slight deformations. Of course the pin plate can be constructed using a photolithography mask taking into account the deformations, but this approach requires image analysis and customized pin plates for each printing tool.

Summary of Invention

[0011] The present invention provides a liquid deposition tool, also called a capillary reservoir device, and methods for depositing a high density biological or chemical array onto a substrate. The tool is made up of a plurality of open ended channels collectively forming a matrix. The matrix has been redrawn and cut such that the pitch of the channels on the loading end is far larger than the pitch of the channels on the liquid delivery end. The upper portion of each channel serves as a reservoir, while the opposing end, which has been formed by the redrawing process, is diametrically sized such that liquid in the reservoir is retained by capillary pressure at the

delivery end. Contained within each channel and running the channel's full length, is a rod. Each rod connects to a rigid template at one end such that when the template is pushed into contact with the input face of the capillary reservoir device, the rod tips housed within the respective channels extend beyond the output face of the device. In operation, each capillary is filled with liquid and when the rod tips are extended beyond the output face, they will each have a droplet of liquid, representative of the liquid held within its respective channel, attached by capillary force to the tip. The droplets are then contacted to a substrate in order to form an array.

Brief Description of the Figures

- 15 [0012] FIG. 1 is a three dimensional view of the capillary reservoir device that is the subject of EPO application #####.
- 20 [0013] FIG. 2 is a partial view of the output face of the capillary reservoir device of the present invention.
- 25 [0014] FIG. 3 is a cross sectional view taken along the line 3-3 of FIG. 2 where the capillary reservoir device is positioned above a substrate.
- 30 [0015] FIGS 4-6 depict a sequence of steps in the process of printing liquid drops onto a substrate, as shown from the same cross-sectional view of FIG 3.
- 35 [0016] FIG. 7 is a three dimensional view of an extruded, sintered, and redrawn form.
- 40 [0017] FIG. 8 is a side view of a reservoir device of the present invention as well as a top view of a section that has been cut from the input end of the device.
- 45 [0018] FIG. 9 is a schematic cross sectional view of the array printing apparatus of the present invention.
- 50 [0019] FIG. 10 is a photograph of the output end of the capillary reservoir device having rods contained within select channels.
- 55 [0020] FIG. 11 is an enlargement of the photograph of FIG. 10 showing four channels, each filled with a rod.
- 60 [0021] FIG. 12 is a sequential series of photographs depicting 4 rods extended from the output face of the capillary reservoir device printing liquid on a substrate surface.
- 65 [0022] FIG. 13 is a top view of a substrate that has an array of liquid droplets printed from the device of FIG. 10.

Detailed Description of the Invention

- 50 [0023] Commonly assigned EPO application EP 98401021.5, incorporated herein by reference, discloses a capillary reservoir device, as shown in FIG. 1, and a method of printing an array of biomolecules. The following description relates to a pin liquid transfer mechanism for use in conjunction with such a tool.
- 55 [0024] The capillary reservoir device 10 of FIG. 1 has a plurality of open ended channels 12 collectively forming a matrix having a top or input face 16, and a bottom or output face 18, of predetermined cross sectional ar-

ea. Each individual channel has continuous and fluid impervious walls defining a liquid reservoir. The cross sectional area of each channel decreases proportionally from top to bottom. The liquid delivery or output end of each channel is sized such that liquid is loaded into each channel through the input face and remains contained within each channel by means of capillary pressure.

[0025] FIG. 2 shows a partial view looking at the output face of a capillary reservoir device from below. Each square region represents the output face 20 of an individual channel. Each round region 22 represents a rod housed within each respective channel. The invention relates to the concept of using these internally housed rods as a means for liquid transfer and delivery to a substrate. Any conceivable substrate may be used in this invention.

[0026] Calibrated wires also called rods are inserted into the input end of each channel of the reservoir device. One end of each rod is immobilized on a movable rear plate, while the other end is cut and polished such that the collective bundle or matrix of rod tips fall within the same horizontal plane. The rod length is set such that when the rear plate moves toward the input face of the reservoir device, the matrix of rod tips are extended a short distance from the device, for example between 150 and 300 μm .

[0027] The rods may be made from any variety of materials. For example, the rods may be made of glass fiber, a metal or a polymer. Preferably, the rods are treated such that the rod tips are wetting while the sides are non-wetting. Such treatments are described in detail in EPO patent application EP 98401021.5, which is incorporated herein by reference.

[0028] The substrate may be biological, nonbiological, organic, inorganic, or a combination of any of these, existing as particles, strands, precipitates, gels, sheets, tubing, spheres, beads, porous beads, containers, capillaries, pads, slices, films, plates, multiwell plates, slides, membranes, etc. The substrate is preferably flat but may take on a variety of surface configurations. For example, the substrate may contain raised or depressed regions on which liquid is deposited. Further the substrate may be glass, polymer or membrane into which channels have been etched; or it may contain regions that have been made porous by means of a chemical etchant. The substrate and its surface preferably form a rigid support on which a liquid with the appropriate surface energy can be deposited.

[0029] FIG. 3 is a cross section view taken along the line 3-3 of FIG. 2. Three channels 30, each containing a different liquid are shown. As an example, each channel may contain an acrylamide solution with a plurality of known distinct oligonucleotides suspended therein. For purposes of illustration, each channel is filled with a different solution 32 in the space not occupied by the rod 22. It should be noted that the rods are located above the meniscus 34 formed by the liquid-channel interface. The goal is to print a droplet of liquid from each

reservoir onto the substrate 36.

[0030] In FIG. 4, each rod 22 has been pushed from the respective channel 30 housing it. The rods are extended by mechanical motion of the rear plate moving toward the input face of the reservoir device. Once extended beyond the output face 42, each rod tip holds a drop 40 of liquid from its respective channel 30 by surface tension. Preferably, the diameter of each of the rods 22 is identical. The rods 22 can be calibrated to consistently deliver predetermined volumes of liquid. The droplets 40 are next contacted with the surface 36 of the substrate as shown in FIG. 5. The rods 22 are retracted back into the channels 30 by pulling the rear plate (not shown) away from the input face of the reservoir device, and a volume of liquid 40 remains on the substrate 36 by means of surface tension, as shown in FIG. 6. Once the rods 22 have been retracted behind the meniscus 34, the tool is ready to print the same array onto another substrate.

[0031] Preferably, the rods all have planar tips that lie within the same plane. However, it is possible to make the rods varying lengths in order to conform to the surface relief features of any substrate. Further, the rods have some space within the respective channel, particularly toward the input end of the device, to flex in order to accommodate imperfections or raised areas on the substrate surface.

[0032] The rods themselves occupy space within the channel that would otherwise contain liquid, but the displaced volume only amounts to approximately between 10% and 50% of the total channel volume, depending on the shape of the channel. Even with the displacement, a 100 μl channel can provide between 500,000 and 900,000 100 μl drop transfers.

[0033] The internal rod actually increases the local capillary pressure within the channel. For example, for a channel that is 120 x 120 μm square, the local capillary pressure can be determined by the formula $P = 2\gamma/r$, where γ is the liquid surface tension and r is the radius of the part of the channel that contains liquid. In the case where the capillary contains only liquid, $r \approx 60 \mu\text{m}$, and $P = 2\gamma/60 \text{ N/m}$. When the capillary contains both liquid and a rod having a radius of approximately 50 μm , $r \approx 15 \mu\text{m}$, and $P = 2\gamma/15 \text{ N/m}$. This demonstrates an approximate fourfold increase in capillary pressure as between the capillary containing only liquid and the same capillary containing both liquid and rod. The increase in capillary pressure aids in the retention of liquid within the channels and helps allow for printing in vertical, horizontal, and inverted positions.

[0034] FIG. 7 and FIG. 8 help illustrate one method for construction of the reservoir device having internal rods. As described in EPO patent application EP 98401021.5, a slurry of particulate glass and an organic binder are extruded through a die forming a multi-celled block preform. The preform is then sintered driving off the binder and consolidating the glass. Next, the resultant sintered form is drawn down such that cross sectional diameter

is significantly reduced, a term of art called "redraw". FIG. 7 shows a form 50 that has been redrawn.

[0035] Once the form has been redrawn, cuts 51, 52 may be made perpendicular to the length of the form to establish the input and output face of the resultant capillary reservoir device. These perpendicular cuts may be made at any point along the form in order to establish any desired diameter for the input and output faces, and in order to accommodate the size of any array. In FIG. 7, cut 52 exposes the input face, while cut 51 exposes the output face.

[0036] In order to make the rear plate, a section cut 54 of the form 50, made just above what is to become the input face of the reservoir device, can be made. What results from these cuts is a disk section whose chambers conform and register exactly with the channels of the reservoir device. In other words, one face of the section piece matches exactly with the input face of the reservoir device. A flat plate is preferably attached to the other face of the section in order to close off the individual chambers within the section. This sectioned piece, also called a rear plate, is set aside while the channels are loaded with rods.

[0037] In an alternative embodiment and as shown in FIGS. 7 and 8, two disks are cut from the form 50 along lines 54 and 55, just above what is to become the input face of the reservoir device 61. The first disk 60 is used as a registration aid, while the second disk 62 is used to make the rear plate. This embodiment is described in more detail below. FIG. 8 further shows the reservoir device having an exposed output face 64 and input face 66.

[0038] Rods are preferably of uniform diameter and sized such that they occupy approximately 80% of the cross sectional area of the output end of the device. They are loaded individually into the input ends of each channel and fed through until each extends beyond the output face. Next, the end of each rod extending from the input face is fitted into a corresponding chamber from the rear plate and fixed in position by epoxy for example. Once all the rods are fixed in place, as the rear plate moves, so move the rods slidably within the channels. The rear plate is next temporarily fixed in position preferably approximately between 150-300 μm , and as far as 1 mm from the input end while the rods are cut so that each rod tip is located within the same plane as the output face of the device. This way, when the rear plate comes in contact with the input face of the device, the rod tips will each be extended an identical distance from the output face. Pulling the rear plate away from the input face causes the rods to be retracted. Ideally, in operation, the rod tips are retracted into the channels past the liquid meniscus that exists within each. They are extended together and contacted with a substrate such that a liquid drop is transferred from the rod tip to the substrate.

[0039] In a preferred embodiment, the rear plate will not come into contact with the input face of the reservoir. Instead, the rods are cut at a length to allow a gap of

500-800 μm between the rear plate and the reservoir while the rods are fully extended from the output end of the device. This gap allows for slight tuning during the printing. The rear plate may be angled by a degree or

5 more from the plane defined by the input face of the reservoir to ensure contact from all rods with the substrate surface. Further, it has been observed that if the reservoir is twisted slightly (preferably between 20°-90°) on its longitudinal axis during redraw. In a reservoir having 10 such a twist, and as the rods are extended from the output end of the device, the rods themselves will exit the channels directly in the center of each opening. This shift allows for more regular and predictable spacing between drops in the array.

15 [0040] In an alternative embodiment, two disks, a registration disk and a rear plate, are cut from the reservoir device as shown in FIG. 8. The rods are threaded either individually or, if the rod is u-shaped, two by two, into the input ends of each channel and fed through the registration disk such that each rod passes through a channel of the reservoir device and the complimentary cell from the registration disk. Similarly, the rods are threaded through the corresponding chamber from the rear plate and fixed in position by epoxy for example. Once 20 all the rods are fixed in place, as the rear plate moves, so move the rods slidably within the channels. The registration disk has two opposing surfaces and is located between the rear plate and the input face of the reservoir device, and is not fixed in place. It is made up of a matrix of open ended cells that register on one surface with the channel openings on the input face of the reservoir device and register on another surface with the chambers of the rear plate. The registration disk can be slidably moved along the length of the rods. The purpose of the 25 registration disk is to allow for insertion of the rod bundle once removed from the reservoir. This way, the collection of rods attached to the rear plate may be removed from the reservoir, to allow for filing of the reservoir, for example. The bundle of rods can be easily fitted back into the channels through the input face of the reservoir device by sliding the registration disk to the end of the bundle opposite the rear plate. This way, the rods are properly spaced in relation to one another and may be simultaneously loaded into the reservoir device. The registration 30 disk will preferably never become detached from the bundle of rods. In this embodiment, the thickness of the rear plate is preferably approximately one-eighth the diameter of the input face of the reservoir, while the thickness of the registration disk is preferably approximately one-fourth the diameter of the input face of the reservoir.

35 [0041] The mechanism for transfer is ideally surface tension on the rod tip. In an alternative embodiment, it is possible to propel a stream of liquid from the channels by mechanical displacement. In this embodiment, the 40 rods are sized such that they occupy greater than 90% of the cross-sectional area of the output face of each channel. The rods perform as pistons and force a quantifiable volume of liquid from each channel. The volume 45

that is propelled out of each channel is a function of the viscosity of the liquid, the distance each rod is retracted, as well as the speed at which the rod is forced forward when dispensing.

[0042] As another alternative, and in cases where the surface energies of the liquid and substrate are incompatible, the substrate may be coated with a metallic layer, gold for example. Electrodes can be attached to the substrate surface as well as the metal rods of the device and the electrical differential may be employed to elicit droplet transfer from the rod tips to the substrate. This way, when the liquid contacts the surface, the circuit is complete and a droplet is deposited.

[0043] FIG. 9 is a cross-sectional schematic view of a capillary reservoir device printing tool employing the liquid transfer mechanism of the present invention 70. The capillary reservoir device 72 is mounted and held fixed by a housing 74. The rear plate 76 is fixed on a slidable mount 78 such that the mount may move back and forth in a horizontal plane. Located between the rear plate 76 and the reservoir device 72 is a registration disk 79. A substrate 80 is lowered into a fixed printing position in front of the output face 82 of the device. An open passage 84 allows an operator to monitor the printing process as seen through the substrate 80 (assuming a transparent substrate). A UV lamp 86 having an unobstructed passage to the substrate is also fixed in position. The UV lamp 86 may be turned on immediately after a UV curable liquid is transferred to the substrate from the device in order to cure the biomolecule containing liquid to the plate before any loss to evaporation. The printing space 90 as defined by the dotted area is preferably an air tight and clean environment, free of any dust or other particulates that may contaminate the array. A shutter is placed over the output end of the reservoir device while the UV lamp is activated in order to prevent the curing of the gel still within the capillaries.

[0044] FIGS. 10-13 are photographs of the tool, the tool in operation, and a substrate after having been affected by the printing process. A sample tool was constructed such that a 6 X 8 array could be printed. FIG 10 shows the output face of the sample reservoir tool. Each channel 92 but one in a 6 X 8 matrix contains a stainless steel wire 94 having a diameter of approximately 140 μm . One channel 96 is left open for identification and orientation purposes. The number of channels within the matrix may be any number; for example to print an array of 10,000 drops in discrete regions, a 100 X 100 channel array would be employed.

[0045] FIG. 11 is an enlarged view of four selected channels from FIG. 10. The on center pitch between any two successive channels is approximately 300 μm in both the horizontal and vertical direction.

[0046] FIG. 12 shows a series of four rods 100 extended from the output end 102 of a capillary reservoir device. Each rod tip contains a volume of liquid 104 as shown in FIG 12A. The rods are further extended until they contact a substrate 106 as shown in FIG 12B. Next,

the rods are retracted leaving a volume of liquid 108 representative of its channel's contents in a corresponding region on the substrate.

[0047] FIG 13 is a top view of the substrate 106 after transfer. A 6 X 8 array results. Each spot 104 contains a volume of approximately 100 μl and the on center pitch between each is approximately 300 μm . It should be noted that no liquid was transferred from the channel 96 that did not contain a rod.

[0048] It should be noted that the capillary transfer mechanism and method described herein has the advantage over a printing mechanism that prints an array one dot at a time in that there is no tolerance buildup. In other words, since the array is printed in one step by contacting all the rods simultaneously on the substrate, the geometric relation of the spots in the array is guaranteed because the on center distances are fixed. The only potential tolerance is the rod position within the individual channel. Conversely, when a robotic spotter device prints one spot at a time, the x, y locations in the array are subjected to software and machine tolerances that potentially may build up as the array is printed. Eventually, such a buildup causes problems with identification and alignment of individual spots.

[0049] It may also be conceived that due to the alignment advantages of the present invention, a multiple print may be performed onto the same substrate. This has applications for combinatorial chemistry. In other words, a first printing may lay down an array of molecules. A second printing may lay down another array directly on top of the first. A reagent may then be added to facilitate reactions between the molecules on each site and the result is an array or library of compounds. Multiple printings and multiple combinations are possible at each discrete position.

[0050] It should also be noted that the capillary transfer device of the present invention should not be limited to the printing of DNA fragments. Any variety of biological or synthetic materials that are capable of being held

within a liquid matrix may be employed by the use of this invention including, but not limited to: cells, phages, viable viral particles, proteins, ligands, epitopes, RNA, synthetic oligonucleotides, peptides, lectins, modified polysaccharides, synthetic composite macromolecules, functionalized nanostructures, synthetic polymers, modified/blocked nucleotides/nucleosides, modified/blocked amino acids, fluorophores, chromophores, chelates, haptens and other binding entities. Additionally, the application of this device is not limited to biological materials, but extends to any chemistry capable of being in liquid form or in a suspension including but not limited to emulsions, particle suspensions, and coacervates.

[0051] Although the invention has been described in detail for the purpose of illustration, it is understood that such detail is solely for that purpose and variations can be made therein by those skilled in the art without departing from the spirit and scope of the invention which

is defined by the following claims.

Claims

1. A device for depositing a high density biological or chemical array onto a substrate comprising:

a plurality of open ended channels collectively forming a matrix having an input face and an output face, each channel having fluid impervious walls;
at least one rod housed within at least one channel and capable of longitudinal movement within said channel;
whereby a liquid is capable of being retained in said at least one channel by capillary force; and,
whereby said rod is capable of delivering a volume of liquid from said at least one channel.

2. The device of claim 1 wherein said rod is capable of extending beyond said output face of said device.

3. The device of claim 2 wherein at least one of said channels is filled with liquid.

4. The device of claim 1 wherein said rods are fixably mounted to a rear plate.

5. The device of claim 4 wherein said rods have tips that are all within the same horizontal plane.

6. The device of claim 4 wherein said rear plate has a plurality of chambers therein that register with the channels from the input face of said matrix.

7. The device of claim 1 wherein said rods have a wetting tip and non-wetting sides.

8. The device of claim 4 further comprising a registration disk having two opposing surfaces located between said rear plate and said input face of said matrix, said registration disk having a corresponding matrix of open ended cells that register with the channel openings on said input face on the first surface and that register with said chambers on the second surface, wherein each said rod passes through a corresponding cell.

9. A printing mechanism for depositing an array of liquid drops comprising:

a plurality of rods connected to a rear plate;
a registration plate having a matrix of open ended cells; and,
wherein each said rod is threaded through a corresponding open ended cell in said registration plate.

10. A method of printing liquid onto a substrate comprising:

5
a) providing the device of claim 3;
b) extending said rod from said channel through said output face such that a drop of liquid from said channel is retained on the tip of said rod; and,
c) contacting said rod with a surface of said substrate.

11. The method of claim 8 further comprising the steps of:

15
retracting said rod within said channel such that said tip contacts said liquid; and
repeating steps (a) - (c) on a surface of a second substrate.

20

25

30

35

40

45

50

55

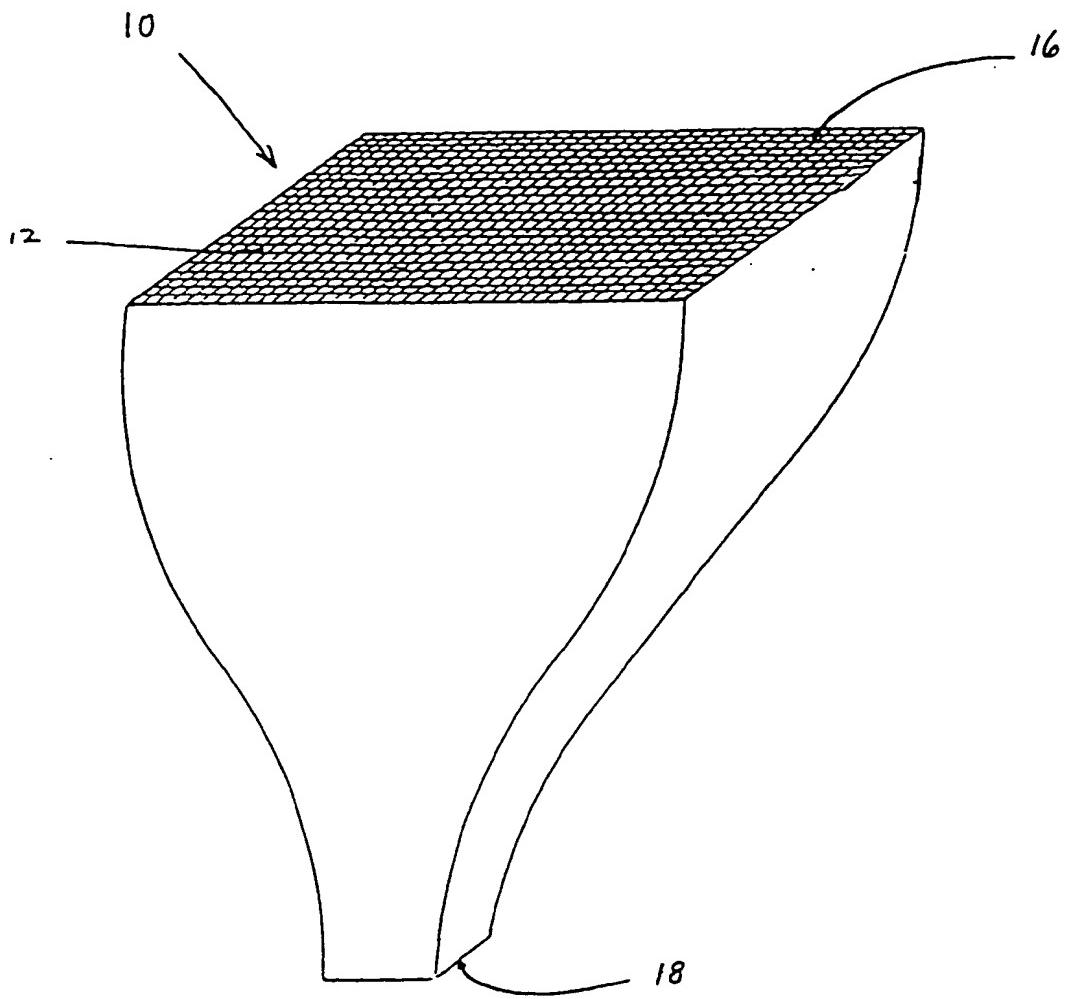


FIG. 1

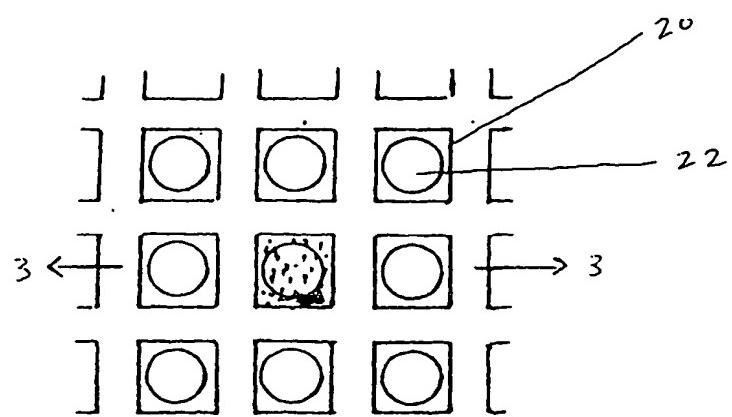


FIG. 2

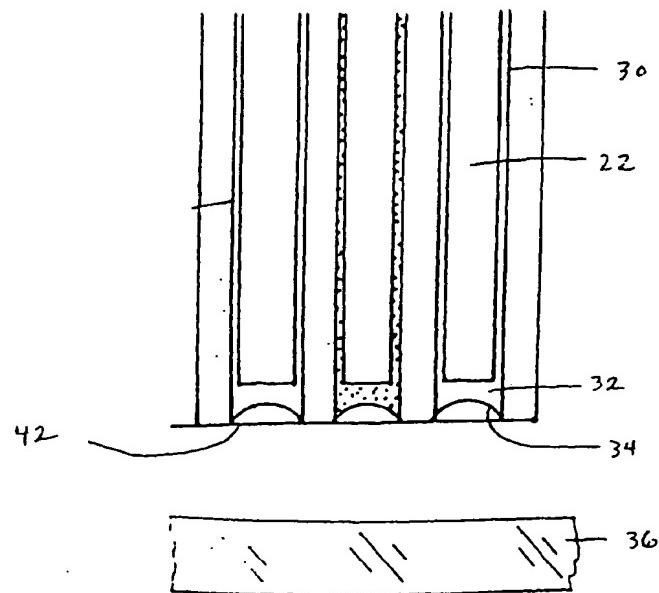


FIG. 3

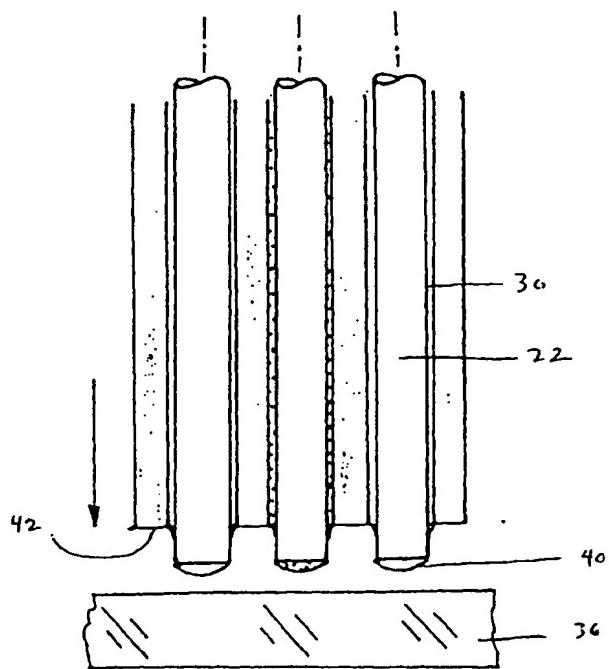


FIG. 4

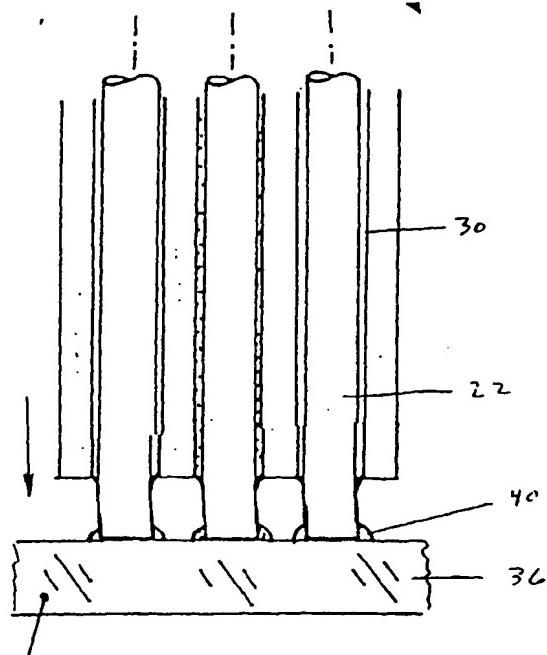


FIG. 5

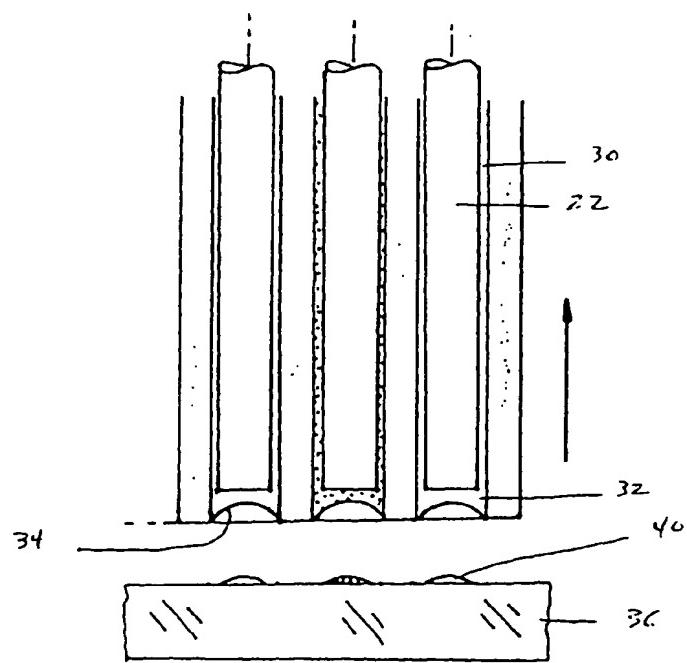


FIG. 6

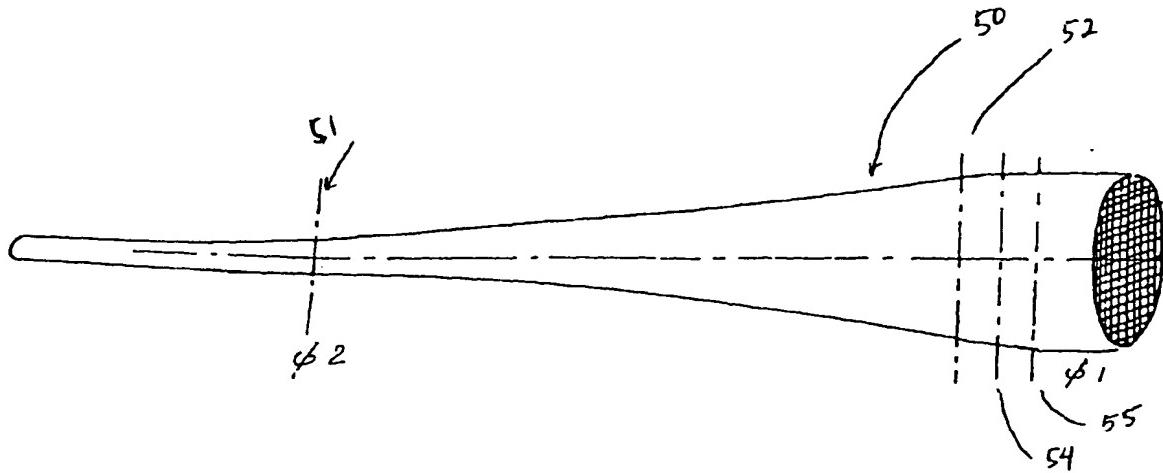


FIG. 7

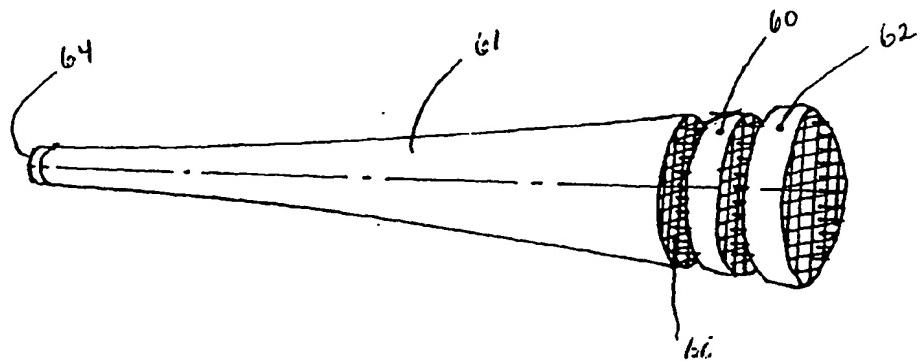


FIG. 8

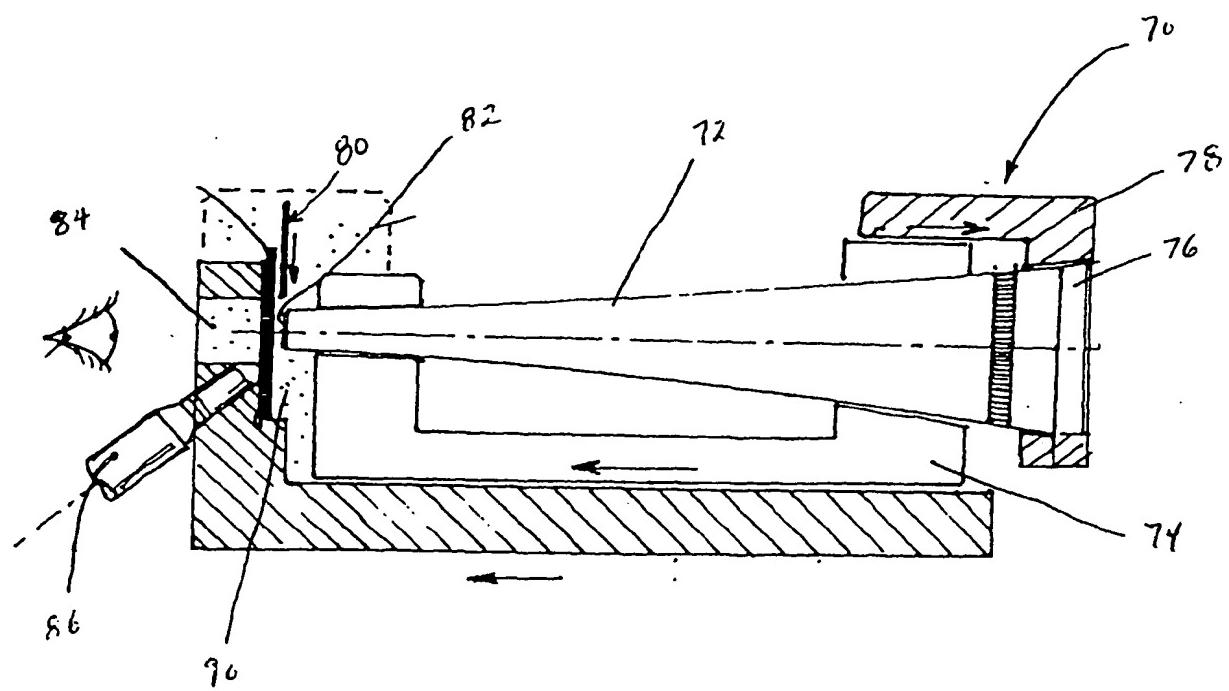


FIG. 9

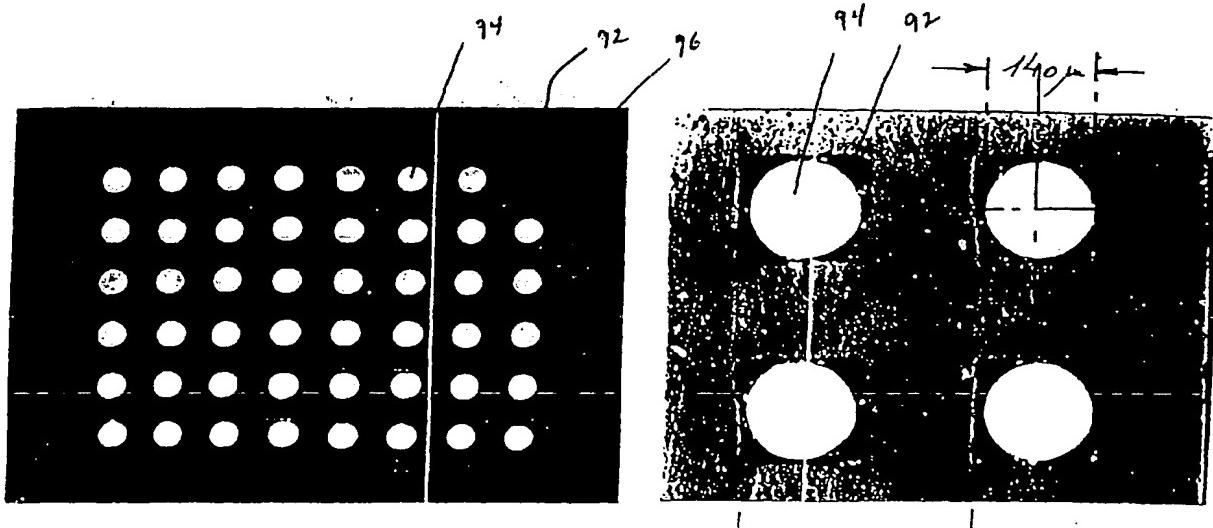


FIG. 10

FIG. 11

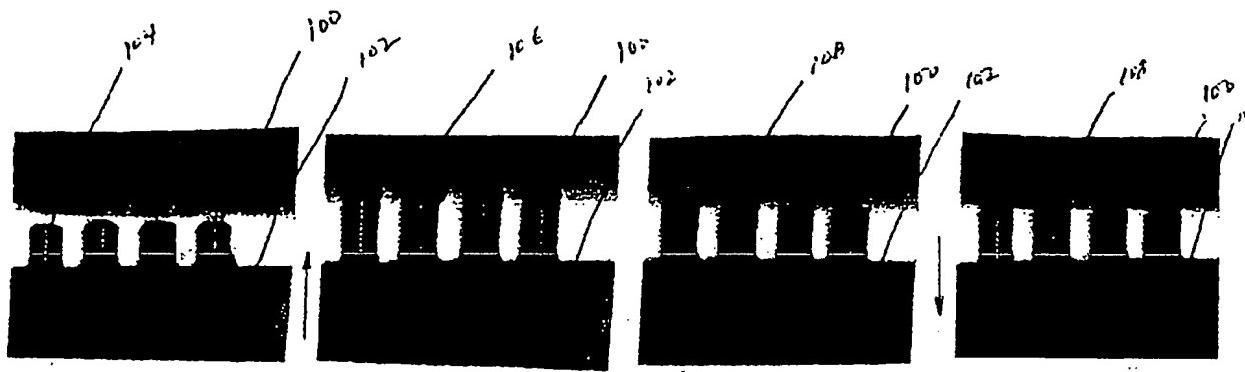


FIG. 12A

FIG. 12B

FIG. 12C

FIG. 12D

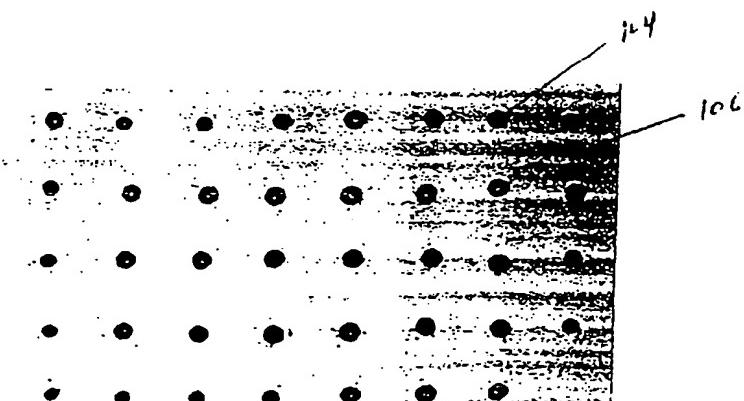


FIG. 13



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 98 40 2906

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	DE 25 46 835 A (PHILIPS PATENTVERWALTUNG GMBH) 28 April 1977 * page 5, last paragraph - page 7, paragraph 1 * * figures 1,2 *	1-3,5	B01J4/02 B01J19/00 B01L3/02 B41J2/23 B41J2/235 B41J2/25 B41J2/265
A	---	4,7,9-11	
A	PATENT ABSTRACTS OF JAPAN vol. 15, no. 125 (E-1050), 27 March 1991 -& JP 03 012944 A (TOKYO ELECTRON LTD.), 21 January 1991 * abstract; figures *	1-3,7,9, 10	
A	PATENT ABSTRACTS OF JAPAN vol. 11, no. 54 (M-563), 19 February 1987 -& JP 61 215066 A (SEIKO EPSON CORP.) * abstract; figures *	1-3,9,10	
A	US 5 551 487 A (GARY B. GORDON ET AL.) 3 September 1996 * the whole document *	1-3,9-11	
A	US 5 508 200 A (THOMAS TIFFANY ET AL.) 16 April 1996 * abstract * * column 7, line 26 - column 8, line 67 * * figures 1,6-10 *	1,3,9-11	B01J B01L B41J
A	WO 98 29736 A (GENOMETRIX INCORPORATED) 9 July 1998 * abstract * * page 21, line 1 - page 29, line 23 * * figures 4,4A,4B *	1,3,10, 11	
	---	-/-	
<p>The present search report has been drawn up for all claims</p>			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	22 April 1999	Stevnsborg, N	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 98 40 2906

DOCUMENTS CONSIDERED TO BE RELEVANT									
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)						
A	US 4 552 716 A (ADOLPH B. HABICH) 12 November 1985 * abstract * * column 5, line 12 - line 17 * * figure 1 * ---	4,5							
A	WO 95 25116 A (CALIFORNIA INSTITUTE OF TECHNOLOGY) 21 September 1995 ---								
A	US 5 265 327 A (SADEG M. FARIS & KANTI JAIN) 30 November 1993 -----								
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)						
<p>The present search report has been drawn up for all claims</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">Place of search</td> <td style="width: 33%;">Date of completion of the search</td> <td style="width: 34%;">Examiner</td> </tr> <tr> <td>THE HAGUE</td> <td>22 April 1999</td> <td>Stevnsborg, N</td> </tr> </table>				Place of search	Date of completion of the search	Examiner	THE HAGUE	22 April 1999	Stevnsborg, N
Place of search	Date of completion of the search	Examiner							
THE HAGUE	22 April 1999	Stevnsborg, N							
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>									

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 98 40 2906

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

22-04-1999

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
DE 2546835	A	28-04-1977	NONE		
US 5551487	A	03-09-1996	NONE		
US 5508200	A	16-04-1996	NONE		
WO 9829736	A	09-07-1998	AU	6646398 A	31-07-1998
US 4552716	A	12-11-1985	AU	564274 B	06-08-1987
			AU	3477984 A	27-06-1985
			BR	8406313 A	08-10-1985
			CA	1208862 A	05-08-1986
			EP	0146001 A	26-06-1985
			JP	1654533 C	13-04-1992
			JP	3018833 B	13-03-1991
			JP	60131257 A	12-07-1985
WO 9525116	A	21-09-1995	AU	701032 B	21-01-1999
			AU	1991995 A	03-10-1995
			CA	2184589 A	21-09-1995
			EP	0750629 A	02-01-1997
			JP	9510452 T	21-10-1997
			US	5847105 A	08-12-1998
US 5265327	A	30-11-1993	US	5565729 A	15-10-1996

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.